Obesity in Childhood and Adolescence: a review in the interface between adipocyte physiology and clinical challenges

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ABSTRACT
Body weight is regulated by a feedback loop in which peripheral signals report nutritional information to an integratory center in the brain. The cloning of the ob gene is consistent with this concept and suggests that body fat content in adult rodents is regulated by a negative feedback loop centered in the hypothalamus. In recent years a number of additional signaling molecules secreted by adipose tissue have been discovered. These hormones, named adipocytokines, include resistin, adiponectin and visfatin. Among the adipocytokines, adiponectin is perhaps the most interesting compound for the clinician since low adiponectin serum levels have been found in obese subjects and in particular insulin resistant patients. The definition and diagnosis of obesity in children and adolescents are surprisingly difficult. The level of fatness at which morbidity increases is determined on an acturial basis. In children and adolescents the degree of body fat mass depends upon ethnic background, gender, developmental stage and age. Treatment and prevention of obesity in childhood and adolescence are major challenges for today’s health care providers and societies.

OBESITY DEFINITION IN CHILDREN
Direct measurements of body fat content e.g., hydrodensitometry, bioimpedance, or DEXA are useful tools only in scientific studies. Body-mass index (BMI) (weight in kilograms divided by the square of the height in meters) is easy to calculate and is correlated sufficiently with direct measures of fatness. BMI is therefore frequently used to define obesity clinically. A child with a BMI above the 97th centile in regard to age and gender is considered to be obese. A child with a BMI greater than the 90th but below the 97th centile would be considered to be overweight. In adults, a BMI greater than 28 kg/m² is associated with an increased risk of morbidity such as stroke, ischemic heart disease, or type II diabetes mellitus. Adults with a BMI greater
than 30 kg/m² are classified as being obese (grade 2 overweight) while those with a BMI between 25 and 29.9 kg/m² are considered to be grade 1 overweight. A BMI over 40 kg/m² is classified as grade 3 overweight. A central distribution of body fat is associated with a higher risk of morbidity and mortality in adulthood.12 The International Obesity Task Force has proposed that the adult body mass index cut-off points (25 and 30 kg/m²) should be linked to body mass index percentiles for children to provide for child cut-off points.1-14 Besides BMI other noninvasive useful clinical measures of obesity are waist circumference, skin fold thickness and waist-to-hip ratio. Waist circumference and waist-to-hip ratio are helpful to assess upper body fat deposition but not provide for measuring visceral-intra-abdominal fat accumulation.

EPIDEMIOLOGY

Projected obesity rates for obesity (BMI > 30 kg/m²) in the adult population of the United States are 20% for the year 2000, 30% for the year 2015, and over 40% for the year 2025.15,16 There is a large increase in BMI in the cohorts with a BMI greater than the 50th percentile. Furthermore, over time, obese children have a tendency towards even more excessive weight. It has become clear that childhood obesity has reached epidemic proportions in all industrialised countries.14 The current age-adjusted prevalence may be as high as 20-30%. In 1999, in a cross-sectional study in the city of Leipzig, Germany, involving more than 2500 children and adolescents between 7 years and 18 years of age, 29% of the subjects were overweight (BMI between 90th and 97th centile, and 16% were obese (BMI above 97th centile). In the same geographical area a large population-based study revealed an incidence of obesity in children and adolescents of around 12%.17

ADIPOCYTE ENDOCRINOLOGY

The discovery of leptin in 1994 opened up a whole field of studies into the biology of adipocytes, their metabolic and endocrine function, and the functional relationships between secretagogues of adipocytes, the so-called adipocytokines, and peripheral metabolic functions.3,4 It is now acknowledged that the sequelae of obesity, particularly diabetes and cardiovascular disease, are influenced to a great extent by the actions of these adipocytokines and that the adipose tissue directly contributes to the pathogenesis of obesity related disorders.

The biology of leptin has been intensely studied, even though the relevance of leptin as an anti-obesity hormone has not been proven at least for humans.18 Resistin was discovered more recently and has generated a good deal of controversy over its function and relevance for humans, and even about its expression by adipocytes. The most coherent effects have been shown for adiponectin, which reveal adiponectin to be the most promising of the adipocytokines with potential impact for the development of therapeutic strategies. However, many other factors derived from the adipose tissue have been discovered, some of them known, such as the cytokines IL-6 or TNFalpha as well as visfatin, a newly discovered product of visceral fat tissue.

LEPTIN

The cloning of the ob gene has greatly advanced our understanding of the mechanism underlying adiposity, eating disorders and reproduction.3 Leptin, a 167-amino acid containing gene product, demonstrates structural similarities with the cytokine family and is mainly produced by the adipocytes. However, recent studies have confirmed that other tissues also express leptin, including placenta, ovaries, skeletal muscle, stomach, pituitary, and liver.18 Leptin acts as an afferent satiety signal regulating appetite and weight in both humans and rodents. It affects central circuits in the hypothalamus, thereby suppressing food intake and stimulating energy expenditure. Thus, leptin plays a major role in the control of body fat stores through coordinated regulation of feeding behaviour, metabolism, the autonom- ic nervous system, and body energy balance. More recent studies revealed direct effects of leptin on the periphery, in part through interactions with other, peripherally acting, hormones such as insulin.

The leptin receptor (Ob-R) is a large single membrane spanning protein and belongs to the gp 130 family of cytokine class I receptors. In mice, at least six alternatively spliced isoforms (OB-Ra,-Rb,-Rc,-
a nocturnal maximum that is not accompanied by commensurate levels in cerebrospinal fluid. Plasma leptin levels are markedly lowered by fasting or dieting and rapidly recovered during refeeding. Leptin expression may also be increased by the actions of insulin, glucose, estrogens, glucocorticoids, TNFalpha, interleukin-1 as well as by conditions of impaired renal function and acute inflammation. A decrease of leptin levels is observed especially in response to beta-adrenoceptor agonists, androgens, cold exposure, thiazolidinediones, and cigarette smoking.

In humans, leptin is encoded by a gene located in chromosome 7q31.3. Congenital leptin deficiency is a rare cause of early onset obesity. To date, only four families with disrupting leptin gene mutations have been identified, three of them of Pakistani origin. Four of the affected children were subjected to recombinant leptin therapy. In all cases this resulted in a dramatic reversal of the phenotype of hyperphagia accompanied by hyperinsulinemia, hyperlipidemia, and other metabolic, neuroendocrine, and immune dysfunctions. Unlike in common obesity, leptin treatment of three leptin deficient adults led to an average weight loss of 18 kg, accompanied by a 58% reduction in energy intake and an increase in 62% in 24-hour fat oxidation in these patients. DNA polymorphisms in the ob gene may be linked to obesity. Sequence variants located in the 5' flanking region of ob gene were found to be associated with obesity or with BMI reduction following a low calorie diet.24,25 Gene variants have also been observed for the human leptin receptor.25-27 A homozygous mutation creating a donor splice site in exon 16 of the ob-r gene and resulting in a truncated leptin receptor lacking both the transmembrane and the intracellular domain has been detected in a consanguineous French family of Karibian origin. Patients with this mutation demonstrated early onset morbid obesity, no pubertal development, and a reduced secretion of hGH and TSH.25 The association between other sequence variations of ob-r and obesity remains controversial in humans. A number of studies now provide evidence that leptin is involved in the pathogenesis of atherosclerotic vascular disease.
In summary, leptin was initially identified as an adipose secretagogue in rodents, that regulates body weight by reporting energy status to the integratory center in the hypothalamus where, consequently, food intake is inhibited. In humans, the situation is different and the weight reducing effects of leptin are not as pronounced. In addition, the biologic role of the circulating leptin receptor/binding protein has not as yet been elucidated. However, many new peripheral actions of leptin have been discovered, underlining that leptin also plays a role in modulating metabolism, energy expenditure, and pathologic processes in humans.

RESISTIN

Resistin, as a novel adipocyte secreted factor with impact on insulin sensitivity, was proposed as a new mechanism to explain the pathogenic sequence adipocyte-obesity-insulin resistance. So far, many aspects of the resistin biology as regards to biological effects and regulation are controversial, and the role of resistin as a mediator of insulin resistance, at least in humans, is questionable. On the other hand, current studies provide evidence for a role of resistin in inflammatory processes, that may be involved in atherosclerosis and thus of relevance also in humans, even though the biology markedly differs between species. Resistin has been independently discovered by three groups through exploitation of different experimental approaches aiming to identify targets of thiazolidinediones, to identify adipose secreted factors by microarray, or as a homolog of inflammatory proteins. Current nomenclature refers to the protein as resistin, and the gene as retn, even though ADSF (adipocyte-specific secretory factor) and FIZZ3 (found in inflammatory zone) are used synonymously. Resistin is a 12.5 kDa cystein-rich peptide that belongs to a family of resistin-like molecules (RELMs) with distinct expression patterns and biological effects. The human peptide consists of 114 amino acids, including a 17 amino acid signal peptide, a variable region of 37 amino acids, and a conserved C-terminus. In all but pertinent studies in humans was found that resistin is not expressed by adipocytes, but high levels of expression and secretion were localized to bone marrow and peripheral mononuclear cells, with lower expression in lung, placental tissue, or pancreatic beta-cells. Serum resistin levels were found to be elevated in rodent models of obesity such as ob/ob-, db/db-mice, or diet-induced obesity, while other and more recent studies found resistin expression and secretion decreased in a variety of obese rodent models. There is slightly more consistent evidence of increased resistin expression associated with insulin resistance in rodents, pointing towards a potential role of resistin in obesity associated insulin resistance.

However, the putative involvement of resistin in obesity and/or insulin resistance in humans is largely controversial. While some studies report positive correlations between resistin and obesity or insulin resistance, others do not find any relationship. The physiological range of serum resistin levels have so far not been characterized, making interpretation of clinical studies difficult. When interpreting data from clinical studies, one needs to consider that resistin may occur in different isoforms that could be differentially detected by the various immunoassays currently applied.

To evaluate biological effects of a compound on the whole organism, experimental animal models are a valuable tool and provide a more detailed insight into resistin biology. Abolishing the resistin gene in mice did not, surprisingly, result in profound phenotypic alterations. Knockout mice had elevated fasting glucose levels but normal glucose tolerance and insulin sensitivity, that were only disturbed when mice were fed a high-fat diet. Chronic elevation of resistin expression and serum levels was achieved by targeted overexpression of resistin in adipose tissue, by implantation of transfected 3T3-L1 cells into nude mice, or by adenovirus mediated chronic overexpression. All these models uniformly show a significantly impaired glucose tolerance and insulin signaling along with hyperinsulinemia and dyslipidemia. Hence, at least in rodents, a role of resistin in mediating insulin resistance syndromes appears feasible. Even though the physiologic and pathophysiologic role of resistin for obesity related insulin resistance in humans is not as evident as it is in the mouse emerging concepts suggest a role for resistin in inflammatory states in humans, which correspond to the predominant expression of resistin.
ADIPONECTIN

The discovery of adiponectin dates back to about the same time as the identification of leptin in 1995/1996, but this adipocytokine did not achieve widespread attention in the scientific community for some years, until its markedly protective role in the pathogenesis of obesity-related disorders was acknowledged. Compared to the aforementioned factors, adiponectin differs in almost all of the biological properties and effects. Nevertheless, so far it has proved the most promising adipocytokine with substantial potential for developing novel intervention strategies for obesity related disorders. Four groups independently identified adiponectin as an adipocyte specific factor that is specifically and abundantly expressed and secreted by adipose tissue. Hence, the nomenclature differed initially with GBP28 (gelatine binding protein 28), ACRP (adipocyte complement related protein), apM1 (Adipose Most abundant Gene transcript 1), and AdipoQ, now, however, commonly referred to as adiponectin. Structurally, adiponectin belongs to the collagen superfamily, sharing homologies with collagens, complement factors, as well as TNF-alpha. The 30 kDa monomer protein of 247 amino acids consists of a hypervariable region following the signal sequence, a collagen-like domain that is important for building secondary and tertiary structure, and a C-terminal globular domain that is responsible for mediating adiponectin effects. Monomeric subunits oligomerize to trimers that further associate through disulphide bonds within the collagenous domain to form bouquet-like polymeric complexes of higher structure including hexameres of app. 180 kDa (low-molecular weight, LMW), and high-molecular weight 16-18 polymers of 400-600 kDa (HMW). These higher order complexes are the predominant forms in human serum. The isoforms differ in their biological function, possibly dependent upon the tissue and receptor isotype. The trimers appeared to confer increased bioactivity, which may suggest that polymers constitute precursors. Only hexameric and higher complexes, however, were shown to be capable of activating the NF-kB transcription factor, suggesting that oligomerization of adiponectin is essential for at least some of its biological effects.

Adiponectin is exclusively expressed by mature adipocytes with increasing expression and secretion during the process of adipocyte differentiation with higher adiponectin mRNA and protein expression in subcutaneous compared to visceral fat. It occurs in remarkably high concentrations in human blood, of about 10 µg/mL, accounting for 0.01% of total serum protein. Males have significantly lower plasma adiponectin levels than females, this sexual dimorphism developing during pubertal development, in relation to serum androgens. Even though adiponectin is exclusively synthesized by adipocytes, adiponectin levels are decreased in obesity, in conditions of insulin resistance and diabetes, and in cardiovascular disease with increasing severity. This reduction in adiponectin appears to precede the disorders, and low adiponectin levels have even been shown to predict the development of type 2 diabetes and cardiovascular disease.

Hence, in summary, these clinical-epidemiological studies and animal studies show uniformly a decrease of adiponectin in obesity, and demonstrate that decreased adiponectin levels, even regardless of body fat mass, confer a substantially increased risk for diabetes and cardiovascular disease, suggesting that adiponectin may even directly contribute to the pathogenesis of these diseases.

The adiponectin receptors were initially identified predominantly on muscle cells (AdipoR1) and liver cells (Adipor2), although in humans they are obviously expressed ubiquitously in the body. Globular and full-length adiponectin bind to both receptors and mediate activation of AMP kinase, PPARα activation, and consequently glucose uptake and fatty-acid oxidation. In the muscle, AdipoR1 was shown to interact with the insulin receptor, thereby enhancing insulin signal transduction, which was one proposed mechanism of adiponectin to ameliorate insulin resistance. In addition, glucose uptake into the cell is facilitated by stimulated expression of glucose transporter-4, further contributing to insulin sensitivity.

In summary, several lines of evidence, consisting of clinical association studies in humans, genet-
As outlined above, using the physiology of adipocytes and adipocytokines a great deal of knowledge has been accumulated as to the pathogenetic mechanisms of obesity and its co-morbidity. Multiple factors are related to the high incidence of childhood obesity. Both genetic/endogenous and environmental/exogenous factors contribute to the development of a high degree of body fatness early in life (Table 1 and Table 2). Twin studies suggest that at least 50% of the tendency toward obesity is inherited. There is also increasing evidence that responsiveness to dietary intervention is genetically determined.

Although a number of monogenetic traits that cause childhood obesity have been identified, in general, a multifactorial aetiopathogenesis of obesity will be present in most patients. Exogenous factors, such as overconsumption of fat-rich diets, lack of physical activity allied with excessive hours of TV watching and computer usage (sedentary lifestyle) heavily contribute to the development of obesity. Nutrition and diet early in infancy is thought to influence growth rate and body fatness beyond infancy. Taking the available data together, many authors support a model in which susceptibility to obesity is determined by genetic factors, but the environment determines individual phenotypic expression.

### Table 1. Factors which contribute to the development of obesity.

**Genetic factors**
- Possibly polymorphisms and/or mutations in any of the following: adrenergic receptors, leptin, Ob-R, SOCS-3, TNF, POMC, MCH, MC4R, NPY, NPY receptors, CRH, CRH receptors, TRH, urocortin, orexin A and B, galanin, neuropeptide, serotonin, prohormone convertase and and many others

**Environmental**
- Increase of sedate activities (TV viewing)
- Lack of and decrease in physical activity
- Shift in diet towards more fast/prepackaged foods with high fat/calory content and/or high sugar content
- Loneliness and social isolation
- Urbanization, housing
- Psychosocial/family problems

**AETIOPATHOGENESIS**

Adipocytes and adipocytokines play a key role in the development of obesity related disorders and the metabolic syndrome, particularly in the pathogenesis of type 2 diabetes and cardiovascular disease. Research has expanded to include a role for adiponectin in cancer and other disease areas. The development of adiponectin analogs holds great promise for the clinical use in improving insulin sensitivity and preventing atherosclerotic disease.
Table 2. Disorders which can present with obesity in childhood - differential diagnosis of obesity disorders.

Endocrine disorders
Cushing’s syndrome
hypothyroidism
growth hormone deficiency
hyperinsulinemia
(pseudo)hypoparathyroidism (Albright’s hereditary dystrophy)

Central nervous system disorders/brain damage
hypothalamic tumor
surgery
trauma
post-inflammation
post-chemotherapy

Genetic syndromes
Prader-Labhard-Willi syndrome
Alstrom syndrome
Bardet Biedl syndrome
Carpenter syndrome
Cohen syndrome

Primary (simple/exogenous) obesity
(multifactorial, multigenetic susceptibility)

CO-MORBIDITY

Among the most common sequelae of primary childhood obesity are hypertension, dyslipidemia, and psychosocial problems. A more complete list of co-morbidity disorders is shown in Table 3. These disorders which arise from overweight and subsequent biochemical changes actually predispose for still additional co-morbidity, such as cardiovascular disease in early adulthood. Since approximately 60-85% of obese children of school age will continue to be obese in adulthood, the co-morbidity factor represents a major health burden in industrialised societies. In addition, childhood obesity seems to increase the risk of subsequent morbidity whether or not obesity persists in adulthood. Most importantly, type 2 diabetes is being increasingly identified in children and adolescents. The clinical picture in children with type 2 diabetes and the fact that most affected patients come from families with type 2 diabetes mellitus have led physicians to conclude that affected children will respond to the same treatments used in adults and that clinical courses

Table 3. Co-morbidities of obesity in childhood and adolescence.

Psychosocial - psychiatric
poor self-image,
social isolation,
autoaggression,
suicide,
promiscuity,
drug and alcohol addiction,
bulimia,
binge eating,
smoking, (enuresis)

Cardiovascular and respiratory
accelerated atherosclerosis,
hypertension
hypoventilation,
sleep apnea,
snoring
Pickwickier syndrome
reduced lung capacity

Endocrine and metabolic
hyperinsulinemia,
insulin resistance,
type 2 diabetes mellitus,
early puberty,
polycystic ovaries,
dysmenorrhea
dyslipidemia,

Orthopedic
slipped capital femoral epiphyses,
coxa vara,
Blount’s disease,
Legg-Calve-Perthes disease
back pain

Others
paronychia,
akanthosis nigricans,
striae rubrae
will be similar to those described in adults.\textsuperscript{1,2,16,17}

**THERAPEUTIC APPROACHES**

Because obesity is a risk factor for numerous medical disorders, psychosocial problems, and excess mortality, it is indeed imperative that effective treatment be developed and be widely available and instigated.\textsuperscript{65-67} Therapeutic strategies include psychological and family therapy interventions, lifestyle/behavior modification and nutrition education. The role of regular exercise and exercise programs is emphasized.

Multidisciplinary outpatient treatments are considered to be the most effective. In most countries, networking of primary care physicians, public health/school medicine institutions, specialists of paediatric and adolescent medicine, social workers, child psychologists and dietitians as well as sports educators could be instituted. Health insurance providers and policy makers should support such networking concepts. Some workers have reported high success rates in the use of such approaches, as well as, sufficient longterm weight reduction in small groups of children studied.

Since the efficacy of the available treatment strategies is still limited, longterm treatment including extended pharmacotherapy may be necessary for the majority of very obese adolescents.\textsuperscript{15,65} At the present time, two drugs are increasingly being employed (orlistat and sibutramine). Orlistat binds to gastrointestinal lipases and causes a partial inhibition of fat resorption from the gut. In contrast, sibutramine causes a centrally mediated increase in satiety and energy expenditure. When combined with a hypocaloric diet, both drugs lead to a moderate additional weight loss of some kilograms within six months.

It is important to note that appetite suppressants and thermogenic drugs have not been approved for use in children. If one is to classify the agents under development according to their main mode of action, there are three main modes to be distinguished, namely, substances that act upon energy intake, energy storage, or energy output. Agents which influence energy intake may either act through the brain by modifying behaviour or be anorexic. In addition, some agents that reduce energy intake exert their actions by altering gastric emptying, causing malabsorption or relay satiety back to the brain. Drugs that modify energy storage either decrease lipid storage or increase lipid oxidation in the fat tissue. Lastly, energy output can be regulated either in the brain or in skeletal muscle and brown adipose tissues.

It is clear that all therapies must be considered within the framework of a multidisciplinary approach with the support of an interdisciplinary team, which has to include paediatricians/internists, psychologists and dietitians.\textsuperscript{2,14}

Children with type 2 diabetes will have to be transitioned to oral antidiabetic agents. Little is known about therapy in children with co-morbid conditions which frequently accompany type 2 diabetes mellitus. Very recently, a multicenter trial of metformin use in children with type 2 diabetes mellitus was completed in the United States. Since metformin also seems to reduce appetite in obese children with type 2 diabetes, it may be beneficial and prove to be the drug of choice in the long term. Side effects include gastrointestinal problems and should not be neglected.\textsuperscript{17}

**Childhood obesity as a major burden for the economy**

The financial burden of childhood obesity for industrialized societies can only be roughly estimated. The annual economic costs due to medical expenses and lost income as a result of complications of adult obesity is approximately 70 billion dollars in the USA. At least another 30 billion dollars are thought to be spent on diet foods, products and programs to lose weight. If one is to calculate the prospective costs of obesity forms that have started at an early age, the prospective financial costs are even higher. Meanwhile, the sales and profits of the obesity treatment industry have reached astronomic proportions. Therefore, obesity in childhood and adolescence has already become a major factor in health care planning systems and within the health care industry as such. Since obesity is associated with a significant increase in morbidity and mortality, it is a major public health burden. Moreover, in addition to the prospect of diminished health, obese peo-
People are often stigmatized both socially and in the workplace. This fact also contributes to the economic cost of obesity, albeit in an unknown and largely indeterminable way. The optimal BMI associated with the greatest longevity is 23 to 25 for whites and 23 to 30 for black adults. For any given degree of overweight, younger people generally have a greater degree of years of life lost than have older subjects.

**PREVENTION**

As prevention has to start very early in life, a population and community scheme for prevention seems to be the most promising and reasonable approach. However, primary prevention has been proven to be difficult or virtually impossible in most societies. Again a multidisciplinary team approach is called for to develop and secure preventive strategies. Good nutrition and modest exercise for pregnant women as well as monitoring of intrauterine growth of the child must be mandatory. After birth, rapid weight gain should be avoided and principles of good nutrition and physical activities should be taught at all ages. Breast feeding should be strongly recommended. Children’s food choices can be influenced by early intervention and guidance. Parents should thus be encouraged to make healthy foods easily available to the child and serve these foods in positive mealtime situations in order to help their child develop healthy food habits. Joint actions by physicians, health authorities and politicians both in the community and also using modern media and mass media are being called upon to implement nation-wide prevention programs. Such programs have to take into account cultural and racial preferences and attitudes in respect to food preparation and eating habits. Taxes on fast foods and soft drinks should be considered, while nutritious foods such as fruits and vegetables could be subsidised for the poorer income classes. Nutrition labels should be required on fast-food packaging. Last but not least, food advertising and marketing directed at children should be banned, while funding for public-health campaigns for obesity prevention should be increased. Recent changes in federal tax laws in the United States may influence health plan roles in promoting physical activity and thus may assist prevention of obesity.

**CONCLUSION**

It is now well known that obesity is the most common chronic disorder in industrialized societies. In some countries, the prevalence of obesity in childhood and adolescence has become higher than that of both asthma and eczema. Childhood obesity is associated with substantial co-morbidity and late sequelae. While diagnostic strategies are clear and straightforward, treatment remains difficult and frustrating both for the patient, family and the multidisciplinary team caring for children with obesity. In our opinion, much more attention should be paid to prevention and the development of preventive strategies at all ages. Prevention should in any case start very early in life. New drugs are being developed that promise to be useful for treatment and secondary prevention. However, sufficient data are not yet available for the use of such agents in childhood and adolescence. Finally, public awareness of the ever-increasing health burden and economic dimension of the childhood obesity epidemic has to be considered by both the public and policy decision makers.

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